Syndrome of the month

The Holt–Oram syndrome

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The classical description of this syndrome of upper limb abnormalities and congenital heart lesions was by Holt and Oram in 1960.[1] They were from King's College Hospital in London and reported a four generation family with nine affected subjects. Many other families were then recognised to have the same condition, which led to a series of reports in the early 1960s. The names atriodigital dysplasia, the heart-hand syndrome, the upper limb-cardiovascular syndrome, the cardiac-limb syndrome, and the cardio-melic syndrome were suggested, but it is the Holt–Oram syndrome that has remained in common use. There have been over 200 cases published and it is found throughout the world. A genetics department in the UK near a cardiology referral centre may expect to see a new family about once every two years.

Clinical details

The features of this syndrome are abnormalities of the upper limbs and shoulder girdle, associated with a congenital heart lesion. The typical combination is considered to be a triphalangeal thumb with a secundum atrial septal defect, but there is a great range in the severity of both the heart and skeletal lesions. The face and lower limbs are normal. Growth and development are within normal ranges.

Skeletal abnormalities

The skeletal abnormalities are found in the upper

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limbs and shoulder girdle. The degree of involvement can range from phocomelia to minor limitation of movement of the thumbs, elbows, or shoulder (figs 1 to 4).

A triphalangeal thumb was reported in Holt and Oram's original paper but, as can be seen in table 1, a range of thumb abnormalities can be found. The thumb may look structurally normal but the patient may be unable to oppose the thumb fully and the thenar eminence may be flat. There maybe a degree of asymmetry with a triphalangeal thumb on one hand
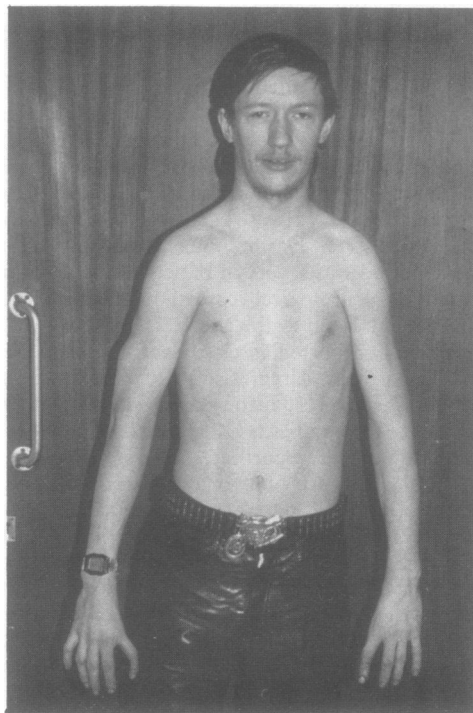

Figure 1   Adult male with Holt–Oram syndrome. Note sloping shoulders, abnormal muscle insertion on right arm, right thoracotomy scar, and thumb abnormalities.
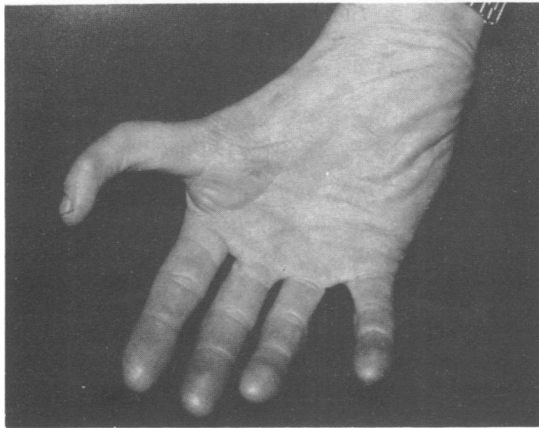
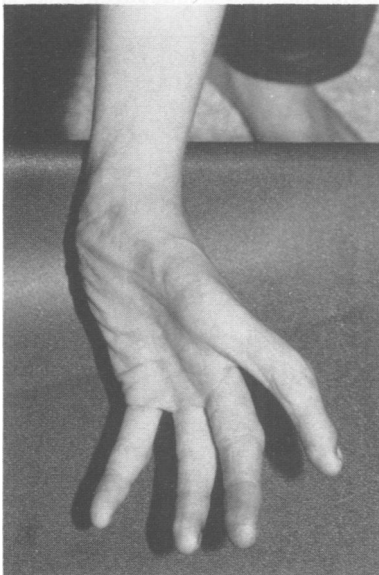Figure 2   Right hand of patient shown in fig 1 showing triphalangeal thumb and flat thenar eminence.

Figure 3   Left hand of patient shown in fig 1 showing absent thumb. A rudimentary hypoplastic digit was removed in infancy.
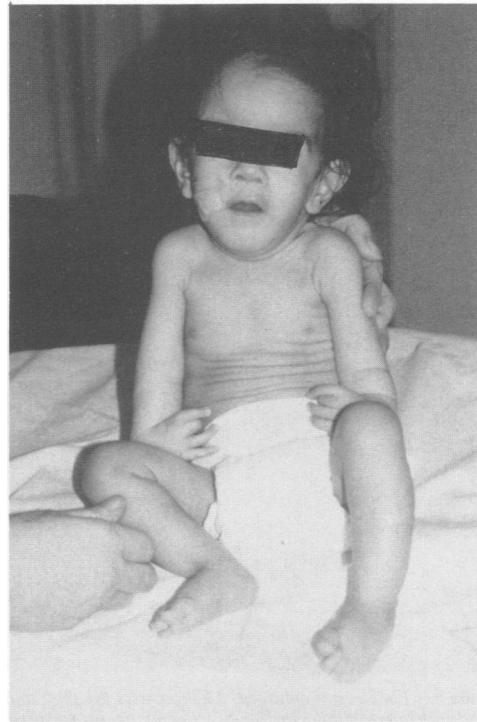

Figure 4   Infant with a severe congenital heart defect and bilateral radial club hands with absent thumbs.

Table 1   Skeletal abnormalities in Holt–Oram syndrome.

	Familial cases (refs 1, 2, 3, 4, 5, and personal cases) (n=43)	Smith et al[5] (n=39*)
Thumb abnormality	38	39
Hypoplastic thenar eminences, non-opposable thumbs	9	
Triphalangeal/digitalised	10	24
Hypoplastic	9	13
Absent	10	16
Hypoplastic radii/short forearms	9	22
Phocomelia	3	6
Minor skeletal changes, normal thumbs	3	0
Normal skeletal examination in obligate carrier	2	0

*Unilateral lesions scored independently.

and a hypoplastic thumb on the other. Partial soft tissue syndactyly of the thumb and index finger is commonly described.

More severe upper limb abnormalities such as phocomelia are easily identified. In the most severely affected patients the humerus is rudimentary or absent and one or two digits are attached directly to the trunk. Phocomelia is found in about 10% of reported patients with Holt–Oram syndrome, though there may be a bias towards selecting patients with severe skeletal lesions. Other upper limb abnormalities found on clinical examination are inequality of arm length, limitation of movement at the elbow (especially of extension, supination, and pronation), and hypoplasia of the musculature, in particular of the deltoids. The shoulders are often described as narrow and sloping with a decreased range of movement. The clavicle may be short, or broad, or show a lateral clavicular 'hook', a feature of any congenital forearm/elbow anomaly (fig 5).
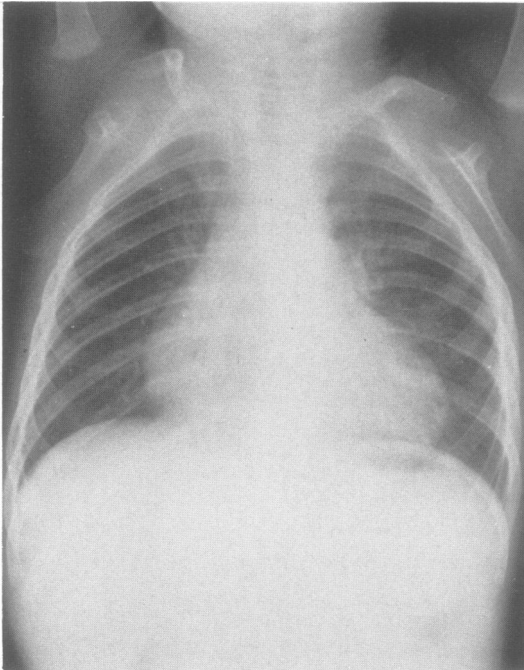
Figure 5 The heart is enlarged. The clavicles are short and broad with lateral clavicular 'hooks'. There is delayed ossification of the upper humeral epiphysis.

RADIOLOGICAL FEATURES

The scapula may be raised and small with abnormalities at the acromial region, a prominent coracoclavicular joint, and a small glenoid fossa. The humerus is hypoplastic or absent in patients with phocomelia. In other patients the medial epicondyles are large and there may be deformity of the humeral head with epiphyseal irregularities (fig 5). Radioulnar and humeroulnar synostosis, radial hypoplasia or absence, and ulnar absence are all reported. The abnormalities of the carpals, metacarpals, and phalanges have been well described by Poznanski *et al.*[7] Scaphoid anomalies are particularly common and include hypoplasia and bipartite ossification. In the normal fetus a carpal bone called the os central (representing a third row of carpal centres) usually fuses with the scaphoid but this may not occur in patients with Holt–Oram syndrome. There may be other additional carpal bones. Other carpal anomalies include absence, hypoplasia, enlargement, irregularity, and fusion. The first metacarpal may have both proximal and distal epiphyses, as may the second to fifth metacarpals, as well as structural changes such as hypoplasia. In general, Poznanski *et al*[7] reports the metacarpals to be larger and the middle phalanges to be shorter than normal. The thumb can be completely triphalangeal or there may be a rudimentary triangular bone between the proximal and distal phalanges.

Alternatively, the thumb can be hypoplastic or absent, it may be attached to the proximal phalanx of the index finger, and it may be bifid (preaxial polydactyly). Other less common skeletal abnormalities include a Sprengel deformity, chest wall anomalies such as deficient pectoral muscles, pectus excavatum or carinatum, and rib and vertebral anomalies (fig 6a, b). There is no association between the severity of the skeletal and cardiac malformations. Smith *et al*[6] reported that the left side was more severely affected, but other authors have not found this. Gall *et al*[8] suggested that females had more severe skeletal malformations than males based on 19 members of a pedigree with 22 living affected subjects.

Cardiovascular anomalies

Those affected in the family reported by Holt and Oram[1] all clinically had secundum atrial septal defects
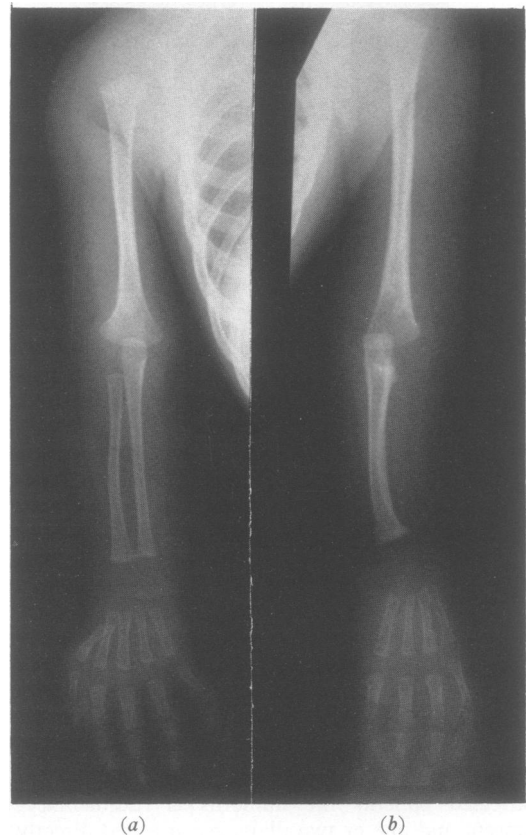

(a)   (b)

Figure 6 Radiographs of upper limbs showing asymmetrical abnormalities. (a) On the right the first metacarpal is hypoplastic and the middle phalanges of the index and little fingers are short. (b) On the left the radius and thumb are absent. The ulna is short and bowed. The middle phalanges of the index and little fingers are short.

Table 2 *Cardiovascular anomalies.*

	Familial cases (refs 1, 2, 3, 4, 5, and personal cases) (n=43)	Smith *et al*[6] (n=39)
Secundum atrial septal defect	20	14
Ventricular septal defect (VSD)	3	9
ECG abnormality but no structural abnormality	2	0
Mitral valve abnormality	1	2
Truncus arteriosus with VSD	1	0
Right isomerism	1	0
Cardiomyopathy	0	1
Atrioventricular septal (AV canal) defect	0	1
Other lesion	0	2
Abnormal but unknown lesion	3	5
Asymptomatic but no full CVS examination	10	0
Normal after CVS examination	2	5

(ASD). Table 2 shows that this is the most common lesion, but ventricular septal defects and conduction abnormalities are frequently found. Disturbances of cardiac rhythm are common in congenital heart disease but in this syndrome the conduction abnormalities may be atypical and may be present in the absence of a structural lesion.

Table 2 compares the cardiac lesions in known families with 39 patients reported by Smith *et al*,[6] in whom over half had a family history. The spectrum of abnormalities is similar in the two groups. A secundum ASD is often associated with abnormalities of venous return such as anomalous pulmonary venous drainage and persistent left superior vena cava. Coronary artery abnormalities have been reported. Two of Holt and Oram's original family had hypoplastic peripheral vessels which prevented cardiac catheterisation and other authors have also found this.[6] Therefore, although the ASD is the most common lesion it is likely that any cardiac malformation could occur in this syndrome.

In the familial group of patients known to have Holt–Oram syndrome, either because of pedigree positions or skeletal abnormality, two patients out of 43 had comprehensive cardiovascular investigations which were all normal. Another 10 were asymptomatic but had not had a thorough cardiovascular examination and investigation.

There has been a suggestion by Gladstone and Sybert[3] that when the mother is the gene carrier then children are more likely to have serious heart malformations.

Natural history

The structural lesions are present at birth. The prognosis depends on the severity of the cardiac lesion. Children with severe limb shortening should be referred to the appropriate local service for consideration of prostheses.

Prenatal diagnosis

Prenatal diagnosis using ultrasound in the second trimester is possible.[9] The radius and ulna are best seen between 13 and 16 weeks' gestation. Minor skeletal abnormalities will not be detected prenatally. A detailed cardiac anomaly scan is usually performed at 18 to 20 weeks. From 16 weeks, the two great arteries, the atria, the ventricles, and the four heart valves can be seen. Severe congenital heart defects can be excluded if these are all visualised and are normal. Anomalies such as septal defects may not be detected. Mothers who have cardiac lesions will require special care during pregnancy. There is some evidence of spontaneous abortion of severely affected fetuses.

Differential diagnosis

The diagnosis is not difficult in the presence of typical clinical features and a family history. In isolated cases the differential diagnosis will include VATER, Roberts syndrome, Fanconi pancytopenia, TAR, and Aase syndromes. Thalidomide embryopathy is an important consideration in young adults whose mothers were treated with this drug in the first trimester.

Inheritance

The syndrome is inherited as an autosomal dominant trait.

In the study of 39 patients of Smith *et al*,[6] 15 were said to have normal parents and were considered to be new mutations. With improvements in the surgical correction of congenital heart lesion the proportion of new mutations is likely to be lower than this. When the diagnosis of the Holt–Oram syndrome has been made in a child it is important to examine both parents before counselling. Clinical examination of the hands, arms, shoulders, and thorax (including heart auscultation) should be performed. Obvious signs may be present but sometimes the significance of minor skeletal abnormalities can be difficult to interpret.

The hands should be examined to detect any thumb abnormalities either in size, shape, or inability to oppose fully. The arm lengths should be compared and forearm supination and pronation tested. The shoulders are often described as sloping and there may be restriction of movement at the shoulder joint. If there are no abnormal clinical signs then radiology is unlikely to help. However, if there are any features, then radiographs should be taken to confirm the clinical suspicion.

Most adults would have had significant heart murmurs detected in infancy and childhood. It is important to ask specifically about a history of a heart murmur. An ECG would detect rhythm disturbances which may be present in the absence of a structural lesion.

If neither parent is affected then recurrence risks for parents (not patient) are small. Known gene carriers have been described with either no cardiovascular or skeletal changes but not without both. Gonadal mosaicism remains a possible cause of recurrence. The severity of the lesion in a parent is no guide to severity in their offspring.

Developmental basis and aetiological factors

Most authors consider that the gene responsible for this syndrome must be active in the embryo at the time of limb bud and cardiac development.[4] Localisation of the gene is not known and no candidate genes have been proposed. Thalidomide can cause a very similar malformation syndrome.

Cytogenetic studies have not found any consistent abnormalities. Rybak *et al*[10] found a deletion in the long arm of a B group chromosome which may be the same as the deletion reported by Ockey *et al*[11] on the long arm of chromosome 4. Turleau *et al*[12] had two patients with a 14q deletion, but other authors of large studies found normal chromosomes in the patients.

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